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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of	:	BAZIN, ET AL.
Serial No.	:	08/472,281
Filed	:	JUNE 7, 1995
Group	:	1816
Examiner	:	GAMBEL
Our File No.	:	61750-142

Assistant Commissioner of Patents
Washington, D.C. 20231

DECLARATION

SIR:

BARBARA E. BIERER, M.D. declares as follows:

1. My curriculum vitae is attached hereto as Exhibit 1.

2. I was requested to review the article by Xia et al., entitled "Rat Monoclonal Antibodies Specific for Human T Lymphocytes," which I have been advised has been relied on as prior art in the referenced application.

3. I was requested to review this publication in order to ascertain whether or not one of ordinary skill in the art, at the time of the publication of this article, would have been able to obtain and identify the antibody referred to in the article as LO-CD2a or an antibody

with binds to the same epitope as the antibody produced by the cell line deposited for this case.

4. Upon such review, I am of the opinion that one of ordinary skill in the art at the time of the publication of the article, or as of March 1993, from the teachings of Xia et al, would not have been able to obtain and identify LO-CD2a monoclonal antibody or an antibody which binds to the same epitope as the deposited antibody.

5. Xia et al. discloses a basic procedure for producing monclonal antibodies, and such procedure produces a plurality of antibodies.

6. I am of the opinion that if one skilled in the art repeated the procedure disclosed by Xia et al., one skilled in the art world would not be able to identify which of the antibodies in the mixture, if any, was LO-CD2a or an antibody which binds to the same epitope as the deposited antibody.

7. Xia *et al.* does not provide information which distinguishes LO-CD2a antibody from CD2 antibodies, as a class, in that the characteristics disclosed by Xia *et al.* are not unique to LO-CD2a.

8. Based on my knowledge of the field, the characteristics disclosed by Xia *et al.* are general characteristics which are possessed by other CD2 antibodies and, therefore, screening antibodies for such characteristics would not indicate whether or not a CD2 antibody was LO-CD2a or whether or not an antibody is an antibody which binds to the same epitope as the deposited antibody.

9. The data presented by Xia et al with respect to LO-CD2a are consistent with the expected characteristics of a CD2 antibody and do not uniquely identify LO-CD2a or an antibody which binds to the same epitope as the deposited antibody.

10. In my opinion, in order to uniquely identify or characterize LO-CD2a, one of ordinary skill in the art would need information with respect to the specific epitope to which LO-CD2a binds. There is no such information in the Xia et al. paper.

11. Although Xia *et al.* indicates that LO-CD2a binds to an epitope which may differ from the epitope to which antibody D66 binds (p. 320), Xia *et al.* does not identify either epitope. As a result, if one skilled in the art, attempted to identify antibodies produced by the procedure disclosed by Xia *et al.*, if D66 is available in the art one skilled in the art could ascertain that a produced antibody does not bind to the same epitope as D66. However, such information would not distinguish LO-CD2a from the plurality of other antibodies which bind to an epitope different than the epitope to which D66 binds.

12. I have reviewed Table 1 of Xia, and based on my experience in the art, the data presented in such Table with respect to LO-CD2a, defines characteristics which are characteristic of CD2 antibodies as a class and does not uniquely identify LO-CD2a or an antibody which binds to the same epitope as the deposited antibody.

13. I have also reviewed the data presented in Figures 1A and 1B of Xia, and such reactivity patterns for LO-CD2a do not distinguish LO-CD2a from CD2 antibodies, as a class. In other words, the characteristics shown in Figure 1A and Figure 1B are characteristics which are not unique to LO-CD2a antibody or which are only present in

antibodies which bind to a specific epitope in that different antibodies which bind to different epitopes possess such characteristics. In fact, such characteristics are of the type found in CD2 antibodies as a class.

14. I note that the reactivity pattern shown in Figures 1A and 1B indicate that the LO-CD2a antibody is not statistically different from a known CD2 antibody; OKT 11.

15. In regard to Table 2, the reactivity with leukemia cells with respect to LO-CD2a is that which would be expected from a plurality of CD2 antibodies whereby such data is not sufficient to uniquely identify LO-CD2a or an antibody which binds to the same epitope as the deposited antibody.

16. In regard to Table 4 of Xia, except for the reactivity with CEM cells, the reactivity pattern of LO-CD2a is similar to a known CD2 antibody, T11. However, it is well-known in the art that other CD2 antibodies have a reactivity pattern such that the CD2 antibody does not react with CEM cells. In this respect, I am familiar with CD2 antibodies which do not react with CEM cells. As a result, the failure of LO-CD2a to react with CEM cells is not a characteristic which uniquely identifies LO-CD2a antibody. In this respect, the Third International Workshop and Conference on Human Leukocyte Differentiation Antigens in Oxford, September 21-26, 1986 (P. 149), reported several CD2 antibodies which did not react with CEM cells, and did react with MOLT4 cells, HPB-ALL cells and Jurkat cells, whereby the reactivity pattern of Table 4 is not unique to LO-CD2a.

17. In regard to Table 5, the rosetting data presented in such table is not unique to LO-CD2a and, therefore, would not uniquely identify LO-CD2a antibody.

18. In regard to Table 6, again, such data is not data which would uniquely characterize LO-CD2a and thereby distinguish LO-CD2a from CD2 antibodies in general.

19. In my opinion, the characteristics disclosed by Xia *et al.* are characteristics which would be possessed by a variety of antibodies. Antibodies having such characteristics do not bind to a single epitope in that such characteristics are those generally present in CD2 antibodies as a class. Those skilled in the art would recognize that the characteristics disclosed by Xia *et al.* are those commonly presented in papers directed to antibodies and do not enable those skilled in the art to uniquely identify LO-CD2a or an antibody which binds to the same epitope as the deposited antibody. Such characteristics may function to indicate that LO-CD2a has characteristics similar to CD2 antibodies and/or to indicate that LO-CD2a differs from antibody D66; however, such characteristics would not be suitable for distinguishing LO-CD2a from other antibodies produced by the general procedure disclosed by Xia, *et al.* or to enable one skilled in the art to identify an antibody which binds to the same epitope as the deposited antibody.

20. I have also been advised that the Examiner has taken the position that one skilled in the art would not reasonably expect an antibody that binds to the same epitope as the deposited antibody to have the same clinical applications and characteristics as the deposited antibody.

21. In my opinion, since it is known in the art that an antibody functions through the epitope to which it binds, one skilled in the art would reasonably expect that two

antibodies, which bind to the same epitope, although not identical in sequence to each other, would have the same clinical applications and characteristics.

22. It is generally accepted in the art that the clinical characteristics of an antibody are imparted by the fact that it binds to a defined epitope, whereby it would be reasonably expected that two antibodies binding to the same epitope would have similar clinical characteristics.

23. In support of the above, as a result of the general acceptance in the art that epitope binding imparts clinical characteristics to an antibody, researchers in the field have devoted significant efforts to characterizing and modeling epitopes of an antibody based on the expectation that the clinical characteristics of the antibody are dependent upon the epitope binding of the antibody.

24. In summary, I am of the opinion that one skilled in the art would reasonably expect that two antibodies which bind to the same epitope would have similar clinical uses and characteristics. Thus, in my opinion, clinical data with respect to a first antibody would cause one skilled in the art to reasonably expect that a second antibody which binds to the same epitope as the first antibody would produce clinical results similar to the first antibody.

25. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

BARBARA E. BIERER

Dated: 9/30/97

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I hereby certify this correspondence is being deposited with the United States Postal Service first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on 9/30/97
(Date of Deposit)
Raymond J. Lillie
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